**SUPPLEMANTARY TABLE 1.** General Characteristics of all patients

| | Parameter | | n=249 |
|---|---|---|---|
| General Condition | Age [years] | | 60 (31 - 82) |
| | Sex [male / female] | | 183 (73) / 66 (27) |
| | Etiology of cirrhosis [alcohol / viral / other] | | 185 (74) / 26 (11) / 38 (15) |
| | BMI [kg/m$^2$] | | 25 (13 - 45) |
| Baseline Scores | MELD§ | | 10 (6 - 25) |
| | Child-Pugh [A / B / C] | | 97 (39) / 70 (28) / 82 (33) |
| | Child-Pugh | | 7 (5 - 12) |
| | CLIF-C AD¥ | | 49 (33 - 67) |
| Baseline Laboratory | Hb [g/dl] | | 12.4 (6.8 - 17.1) |
| | WBC [G/l]¥ | | 7 (1.8 - 23.3) |
| | Platelets [G/l]† | | 150 (29 - 647) |
| | Sodium [mmol/l] | | 137 (114 - 146) |
| | Creatinine [mg/dl] | | 0.9 (0.4 - 2.7) |
| | Bilirubin [mg/dl]§ | | 1 (0.1 - 12.7) |
| | ALT [U/l]§ | | 30 (7 - 311) |
| | Albumin [g/l]§ | | 32 (15 - 47) |
| | INR§ | | 1.3 (0.9 - 2.6) |
| Baseline Clinical | Ascites [no / yes] | | 128 (51) / 121 (49) |
| | Esophageal Varices [no - grade I / grade II - III] | | 193 (78) / 56 (22) |
| Outcome | Mortality 1-year / overall | | 39 (16) / 88 (35) |
| | Fatal ACLF development 1-year / overall | | 21 (8) / 52 (21) |
| | Time to fatal ACLF development [months] | | 17 (0 – 137) |
| | Follow Up time [years] | | 3 (0 - 15) |
| Biomarkers | IL-1α | [Undetectable / detectable] | 187 (75) / 62 (25) |
| | | Detectable [pg/ml] | 69.8 (8.5 – 1573.8) |
| | IL-1β | [Undetectable / detectable] | 172 (69) / 77 (31) |
| | | Detectable [pg/ml] | 73.8 (4.1 – 1180.5) |

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALT, alanine transaminase; AP, alkaline phosphatase; BMI, body mass index; CLIF-C (European Foundation for the study of chronic liver failure consortium); Hb, hemoglobin; IL, interleukin; INR, international normalized ratio; MELD, Model for end-stage liver disease; WBC, white blood cells.

Data are expressed as median (range) or absolute frequency (percentage)

§Data available in 246 patients, †Data available in 245 patients, ¥Data available in 231 patients

**SUPPLEMENTARY TABLE 2.** ELISA kits and limits of detection

| Interleukin | Kit | Range of detection (pg/ml) |
|---|---|---|
| IL-1α | Human 1L-1alpha/IL1-1F DuoSet® ELISA (DY200-05) | 7.81 – 500 |
| IL-1β | Human IL-1beta/IL-1F2 DuoSet® ELISA (DY201) | 3.91 – 250 |

Abbreviations: IL, interleukin

**SUPPLEMENTARY TABLE 3.** Interleukin baseline levels stratified by time era and MELD.

| MELD ≤ 11 | 2002-2011 n=31 | 2012-2016 n=98 | *p* |
|---|---|---|---|
| IL-1α | 34.6±72.0 | 35.0±93.3 | 0.981 |
| IL-1β | 53.1±131.8 | 45.3±151.2 | 0.797 |

| MELD > 11 | 2002-2011 n=44 | 2012-2016 n=77 | *p* |
|---|---|---|---|
| IL-1α | 95.4±267.4 | 48.9±129.4 | 0.210 |
| IL-1β | 100.3±218.7 | 80.3±183.1 | 0.361 |

Abbreviations: MELD, model for end-stage liver disease.

**SUPPLEMENTARY TABLE 4.** Detailed cause mortality in Compensated and Recompensated cirrhosis

| Cause of death n(%) | All patients n=89 | Compensated n=30 | Recompensated n=59 |
|---|---|---|---|
| ACLF | 52 (58.5) | 14 (46.6) | 38 (64.4)* |
| HCC | 5 (5.6) | 2 (6.7) | 3 (5.1) |
| Other cancer | 5 (5.6) | 2 (6.7) | 3 (5.1) |
| Cardiovascular | 13 (14.6) | 6 (20.0) | 7 (11.8) |
| Unknown/Other | 14 (15.7) | 6 (20.0) | 8 (13.6) |

*p<0.05; Abbreviations: ACLF, acute-on-chronic liver failure; HCC, hepatocellular carcinoma.

**SUPPLEMENTARY TABLE 5.** Triggers of fatal ACLF

| Fatal ACLF trigger n(%) | All patients n=52 | Compensated n=14 | Recompensated n=38 |
|---|---|---|---|
| Infection | 13 (25.0) | 3 (21.5) | 10 (26.3) |
| Bleeding | 6 (11.5) | 1 (7.1) | 5 (13.2) |
| Unknown | 33 (63.5) | 10 (71.4) | 23 (60.5) |

Abbreviations: ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome

**SUPPLEMENTARY TABLE 6.** Interleukin baseline levels stratified by fatal ACLF development

| Interleukin level | | Fatal ACLF development n=52 | No Fatal ACLF development n=197 |
|---|---|---|---|
| IL-1α | [Undetectable / detectable] | 33 (63) / 19 (37) | 154 (78) / 43 (22) * |
| | Detectable [pg/ml] | 117.2 (19.3 – 1573.8) | 45.6 (8.5 – 723.5) |
| IL-1β | [Undetectable / detectable] | 30 (58) / 22 (42) | 142 (72) / 55 (28) * |
| | Detectable [pg/ml] | 191.9 (4.3 – 1036.1) | 53.7 (4.1 – 1180.5) * |

IL, interleukin, *if $p<0.05$

**SUPPLEMENTARY TABLE 7.** General characteristics and interleukin-1β levels and detection rate of the external cohort 1 admitted for recompensation of acute decompensation stratified by development of ACLF

| | Parameter | no ACLF development n=32 | ACLF development n=16 |
|---|---|---|---|
| General Condition | Age [years] | 58 (18-79) | 66 (29-80) |
| | Sex [male / female] | 17 (53) / 15 (47) | 10 (63) / 6 (37) |
| | Etiology of cirrhosis (alcohol / viral / other) | 17 (53) / 5 (16) / 10 (31) | 10 (63) / 2 (12) / 4 (25) |
| Baseline Scores | MELD | 9 (7-20) | 9 (6-26) |
| | Child-Pugh [A / B / C] | 6 (19) / 24 (75) / 2 (6) | 2 (12.5) / 12 (75) / 2 (12.5) |
| | Child-Pugh | 8 (5-12) | 8 (6-11) |
| | CLIF-C AD | 45 (23-65) | 50 (33-72)* |
| Baseline Laboratory | Hb [g/dl] | 10.2 (7.8-13.3) | 10.1 (8.2-15.9) |
| | WBC [G/l] | 5.7 (2.4-15.6) | 5.5 (3.7-13.7) |
| | Platelets [G/l] | 118 (46-209) | 145 (39-234) |
| | Sodium [mmol/l] | 139 (130-145) | 137 (121-143) |
| | Creatinine [mg/dl] | 1.0 (0.5-2.6) | 1.0 (0.6-7.6) |
| | Bilirubin [mg/dl] | 0.9 (0.2-4.4) | 0.9 (0.3-4.8) |
| | ALT [U/l] | 27 (14-121) | 24 (6-44) |
| | Albumin [g/l] | 33.4 (17.2-40.0) | 28.0 (17.5-40.8) |
| | INR | 1.1 (1.0-1.5) | 1.1 (1.0-1.4) |
| Bio-marker | IL-1β [Undetectable / detectable] | 21 (66) / 11 (34) | 5 (31) / 11 (69)* |
| | IL-1β Detectable [pg/ml] | 0 (0-43.7) | 1.9 (0-2.9)* |

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALT, alanine transaminase; CLIF-C (European Foundation for the study of chronic liver failure consortium); Hb, hemoglobin; IL, interleukin; INR, international normalized ratio; MELD, Model for end-stage liver disease; WBC, white blood cells.
Data are expressed as median (range) or absolute frequency (percentage)
*$p<0.05$

**SUPPLEMENTARY TABLE 8.** General characteristics and interleukin baseline levels of the external cohort 2 with acute decompensation stratified by presence of ACLF at time of admission

| | Parameter | No ACLF N = 101 | ACLF N = 178 |
|---|---|---|---|
| General condition | Age (years) | 59 ± 12 | 57 ± 11* |
| | Sex [male / female] | 58 (57) / 43 (43) | 114 (64) / 64 (36)* |
| | Etiology of cirrhosis (alcohol / viral / other) | 40 (40) / 36 (36) / 25 (24) | 100 (56) / 46 (26) / 32 (18)* |
| Scores | Child-Pugh | 9 ± 7 | 11 ± 2*** |
| | MELD | 16 ± 6 | 27 ± 7*** |
| Baseline Laboratory | WBC (x10$^9$/L) | 6.2 ± 3.1 | 9.7 ± 7.4** |
| | Platelet count (x10$^9$/L) | 90.9 ± 47.9 | 95.3 ± 65.6 |
| | Serum creatinine (mg/dL) | 1.2 ± 0.6 | 2.4 ± 1.6*** |
| | Serum bilirubin (mg/dL) | 5.1 ± 7.3 | 11.2 ± 11.4*** |
| | INR | 1.6 ± 0.5 | 2.0 ± 0.9*** |
| | Albumin (g/dL) | 2.8 ± 0.6 | 2.9 ± 0.7 |
| Interleukins | IL-1α [Undetectable / detectable] § | 66 (67) / 33 (33) | 68 (40) / 108 (60)*** |
| | IL-1β [Undetectable / detectable] † | 91 (92) / 8 (8) | 150 (84) / 28 (16)** |

Abbreviations: ACLF, acute-on-chronic liver failure at admission; no ACLF, no acute-on-chronic liver failure at admission; IL, interleukin; INR, international normalized ratio; MELD, model for end-stage liver disease; WBC, white blood cells.

Data expressed as mean ± SEM or absolute frequency (percentage).

§Data available in 275 patients, †Data available in 277 patients

IL-1α and IL-1β data show absolute number (percentage) of patients with detectable and undetectable levels

***if $p<0.001$, **p<0.01, *$p<0.05$

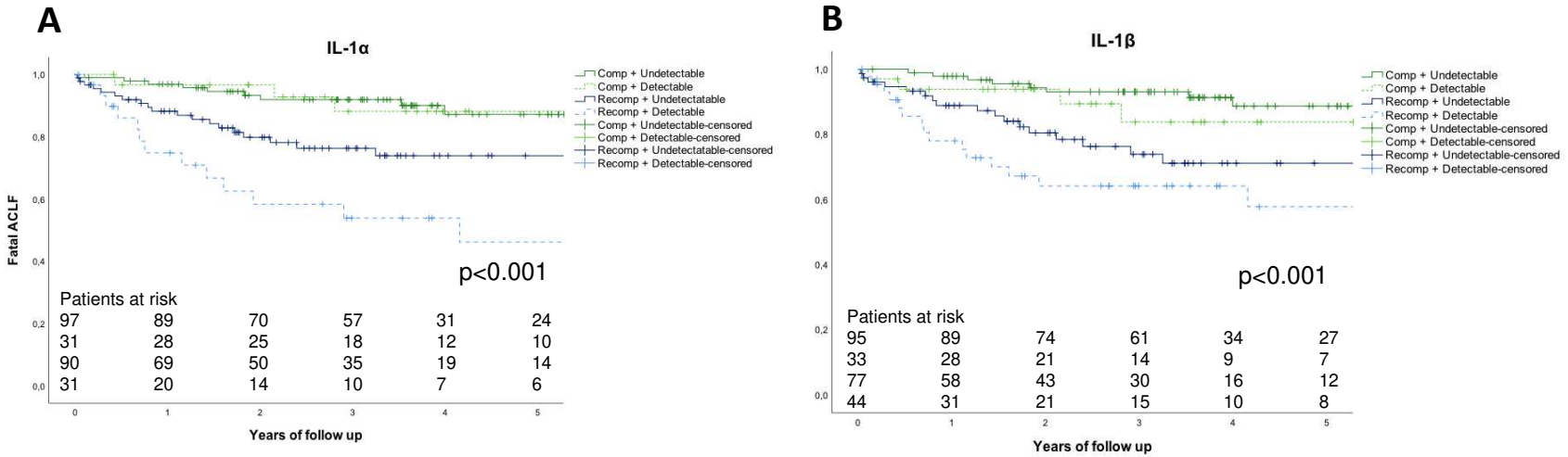
**Supplementary Material 1.**

LPS administration is used to study organ-specific (e.g. neural/renal inflammation), as well as systemic inflammatory response and therefore is well characterized in rodents without cirrhosis. Thus, studies investigate either the acute or long-term response to LPS. Increased levels of IL-1α and IL-1β are detected in liver tissue of rats 30 minutes after injection of LPS (Sang et al. Archives of Biochemistry and Biophysics; 1999) and a peak in serum levels is reached 2-6 hours after injection (Dzhalilova, J Inflamm Res, 2019; Chensue et al. American Journal of Pathology, 1991).

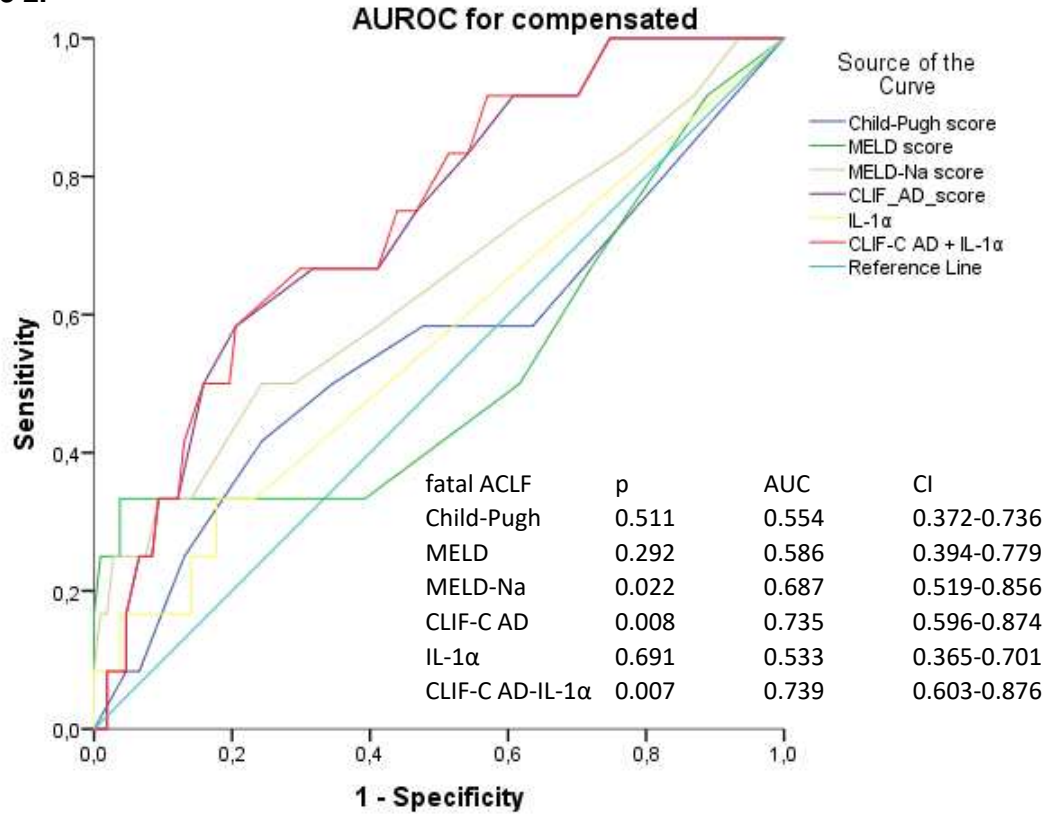
Interestingly, IL-1α and IL-1β expression returns to baseline 18 hours after single LPS administration in hepatic sinusoidal macrophages, as well as 24 hours after LPS in serum. Several studies indicate a fast recovery of the LPS-induced inflammatory state (Bozadas et al. Folia Neuropathol, 2019) when LPS was administered as a single dose. Nevertheless, the extent of the inflammatory response as well as the survival rates are directly associated with the chosen dose of LPS (Thomas, Peptides, 2014; Ranneh et al. Arch Immunol Ther Exp, 2019).

Therefore, we investigated the short- and long-term effect of a sublethal dose of LPS to mimic AD and recompensation in cirrhosis. To our knowledge, this is the first study describing an acute (AD) as well as a chronic (recompensation) change in expression profile of Il-1α and Il-1β pathway after LPS stimulation in liver cirrhosis.

**Supplementary Figure 1.**

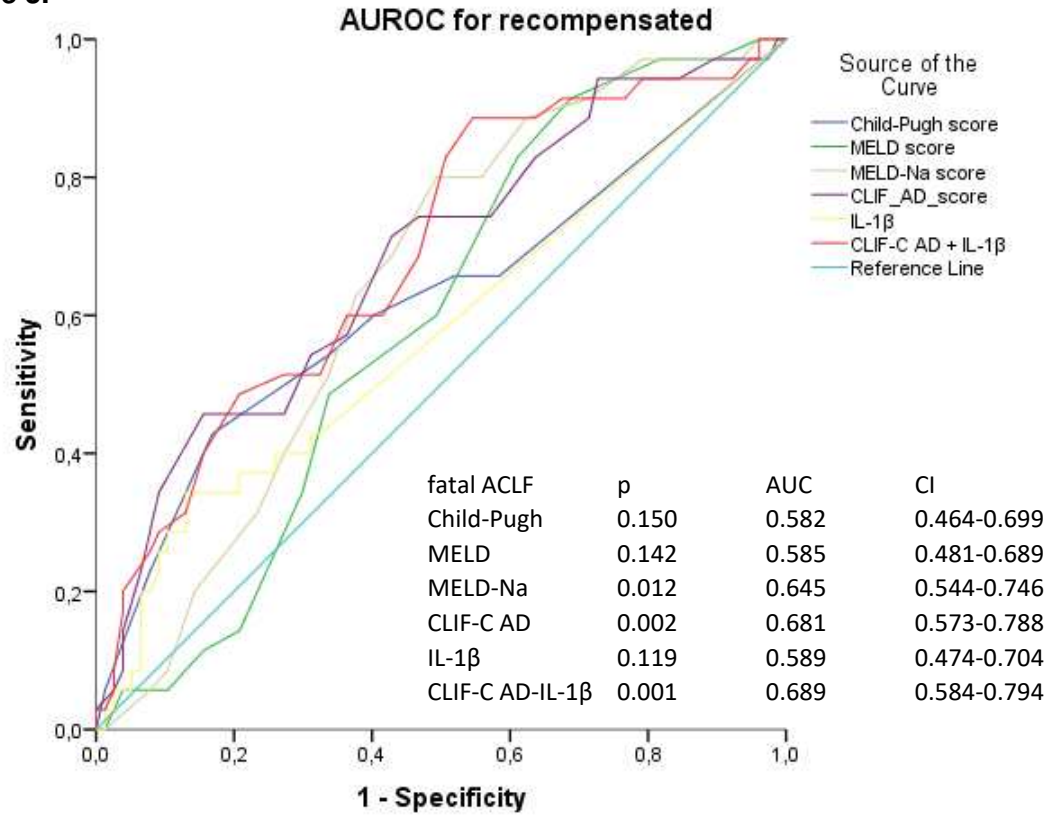


**Supplementary Figure 2.**




| fatal ACLF | p | AUC | CI |
|---|---|---|---|
| Child-Pugh | 0.511 | 0.554 | 0.372-0.736 |
| MELD | 0.292 | 0.586 | 0.394-0.779 |
| MELD-Na | 0.022 | 0.687 | 0.519-0.856 |
| CLIF-C AD | 0.008 | 0.735 | 0.596-0.874 |
| IL-1α | 0.691 | 0.533 | 0.365-0.701 |
| CLIF-C AD-IL-1α | 0.007 | 0.739 | 0.603-0.876 |

**Supplementary Figure 3.**




| fatal ACLF | p | AUC | CI |
|---|---|---|---|
| Child-Pugh | 0.150 | 0.582 | 0.464-0.699 |
| MELD | 0.142 | 0.585 | 0.481-0.689 |
| MELD-Na | 0.012 | 0.645 | 0.544-0.746 |
| CLIF-C AD | 0.002 | 0.681 | 0.573-0.788 |
| IL-1β | 0.119 | 0.589 | 0.474-0.704 |
| CLIF-C AD-IL-1β | 0.001 | 0.689 | 0.584-0.794 |

**Supplementary Figure 4.**